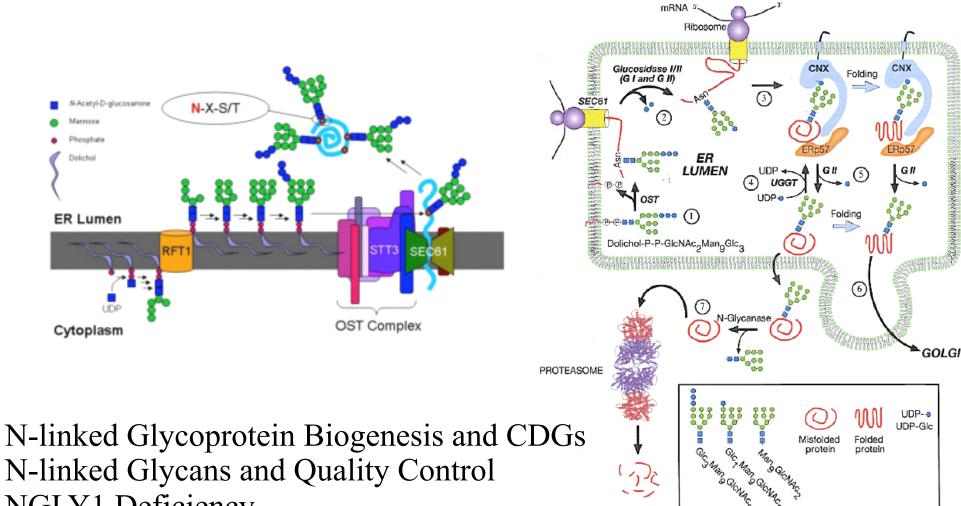
Glycoprotein Diseases: Important, Unrecognized and Challenging



- NGLY1 Deficiency
- Clinical Features of NGLY1 Deficiency (Lynne Wolfe)
- Mannose Oligosaccharide Glucosidase Deficiency (Sergio Rosenzweig)

NIH Glycosciences: A rich and lasting heritage

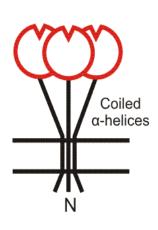




Claude Hudson
The founder of basic
carbohydrate research
at the NIH (Chief-1952)



Hewitt G. Fletcher Chief, 1951-1973





G. Gilbert Ashwell
Discovery of Mammalian Lectins
Chief, LBM, 1978-1983



Elizabeth Neufeld Chief, GBB 1979-1983



Victor Ginsburg Chief, Lab Structural Biology 1986-1991



Roscoe Brady
NINDS
1972 to 2006

Glycoscience Interest Group Undiagnosed Disease Program

Kids who don't cry: New genetic disorder discovered

By Jacque Wilson, CNN

Updated 2:53 PM ET, Thu March 20, 2014











Grace Wilsey was born with NGLY1 deficiency, which is caused by two mutations in the NGLY1 gene.



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MEDICAL DISPATCH | JULY 21, 2014 ISSUE

ONE OF A KIND

What do you do if your child has a condition that is new to science?

BY SETH MNOOKIN













MEDICAL DEPATCH

ONE OF A KIND

After the periods of power while how constition after it were to extend?

BY STREMNOORN

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Destrumity, Bereinst Wight was the only house passes with corner greek dands. His percent toget working for other

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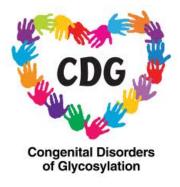


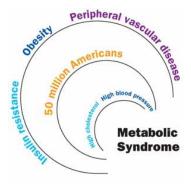
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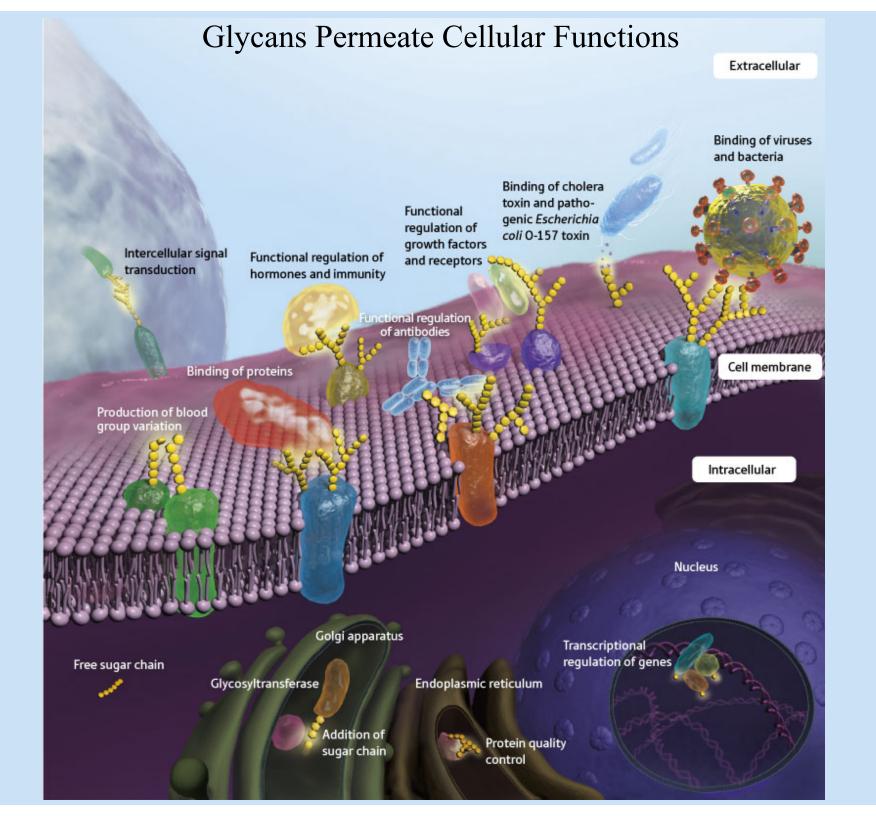
Glycans play a major role in human disease:

- > Rarity/Severity of genetic diseases highlight importance of glycans
- Some Examples of Glycans and Disease:
 - 5 Defective O-glycosylation in Muscular Dystrophy
 - 5 O-GlcNAcylation: Diabetes, Alzheimer's, Cancer, Heart Disease.
 - s Notch Signaling by Glycans
 - **Selectins and Inflammation**
 - s Siglecs and Regulation of Immunity
 - s Galectins role in immunity
 - s Proteoglycans: growth factors, microbe binding, morphogenesis
 - s Microbes and Viruses: Glycans role in entry and defense
 - s Heparin this 'drug' is a GAG.
 - **Monoclonal Therapeutics Glycoforms**
 - s Cell Surface Glycans in Tumor Metastasis Cancer Biomarkers.
 - **Vaccines to Infectious Organisms Many (Most) are glycans.**

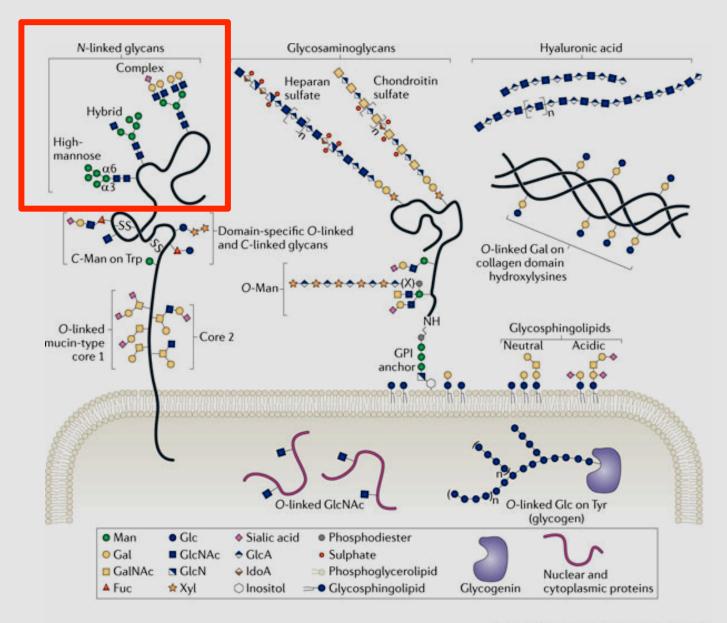






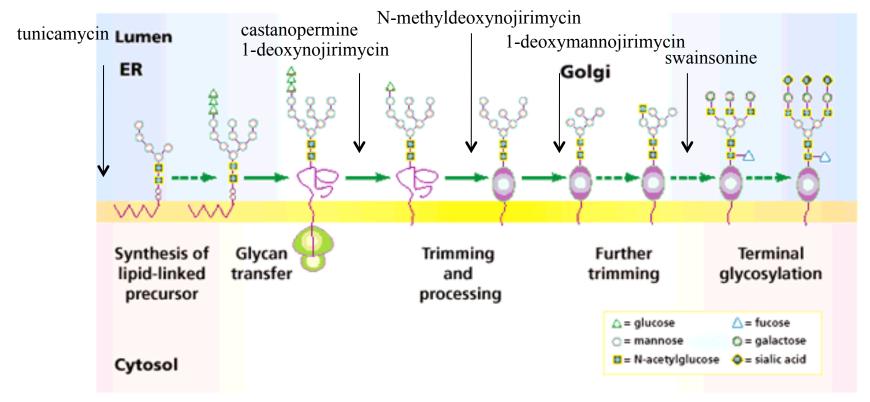


Mammalian Glycoconjugates



N-Glycan Biosynthetic Pathway: A System to Generate Diversity.

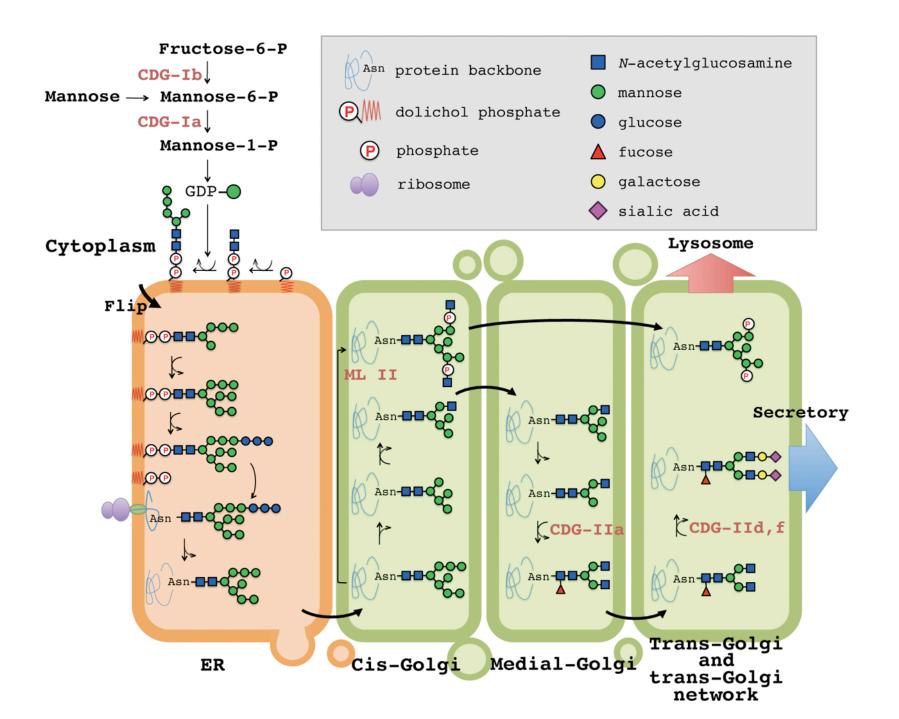
What do we know?



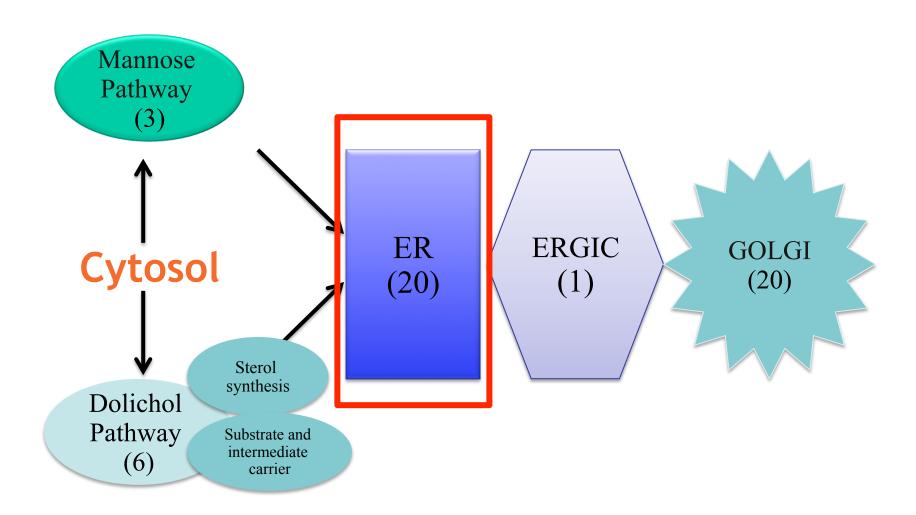
How did we learn it?

- 1. Biochemistry
- 2. Inhibitors
- Yeast and Somatic Cell genetics
- 4. Congenital Disorders of Glycosylation

Glycoprotein Biogenesis and the Congenital Disorders of Glycosylation

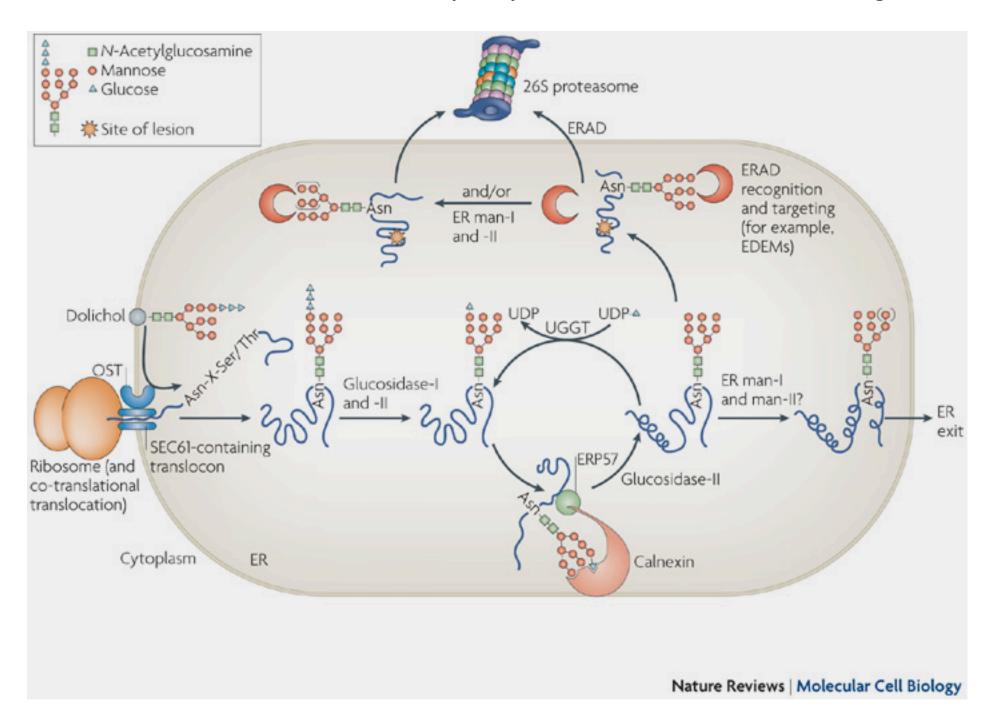


CDG Disorders by Compartment

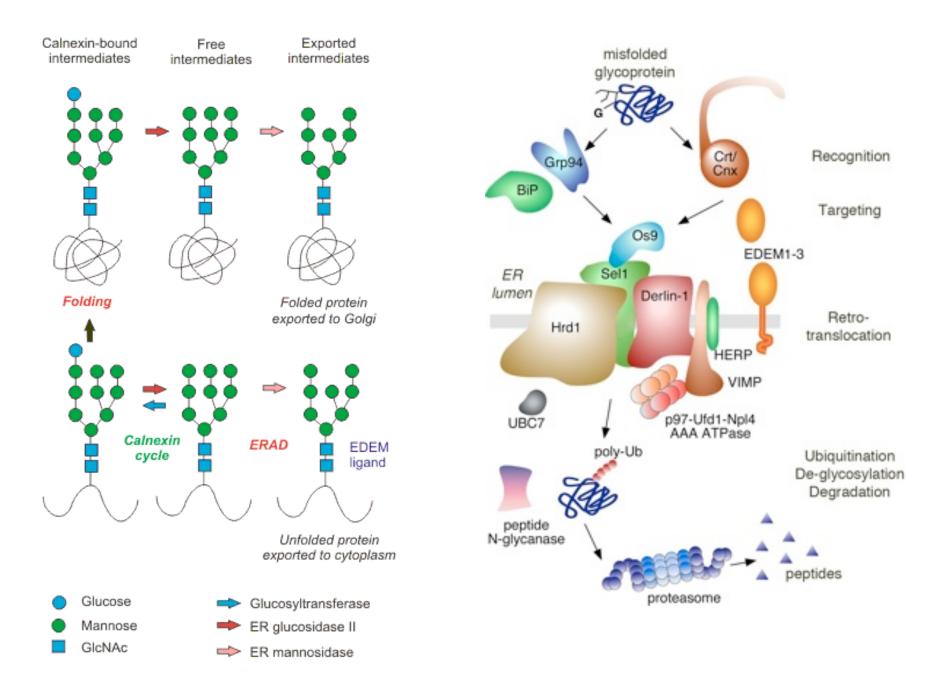


Adapted from J Inherit Metab Dis (2011) 34:853-858 Thanks to Lynne Wolfe NP and Donna Krasnewich, MD, NGMS

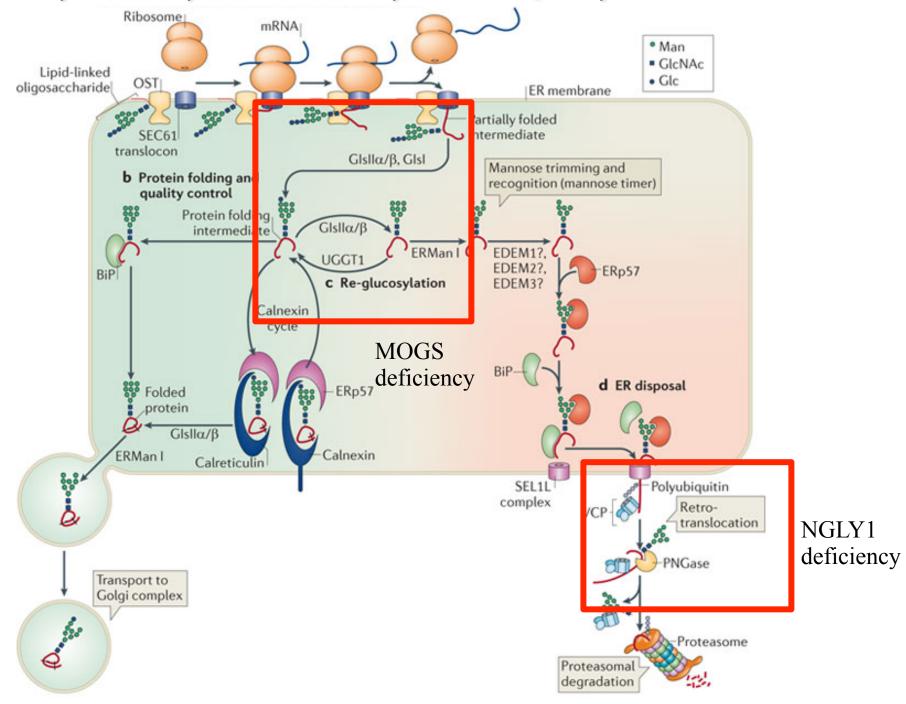
The essential role of N-Glycosylation in ER Protein Folding



N-Glycans in Protein Folding Cycle and ERAD



N-Glycan Biosynthetic Pathway and ER Quality Control





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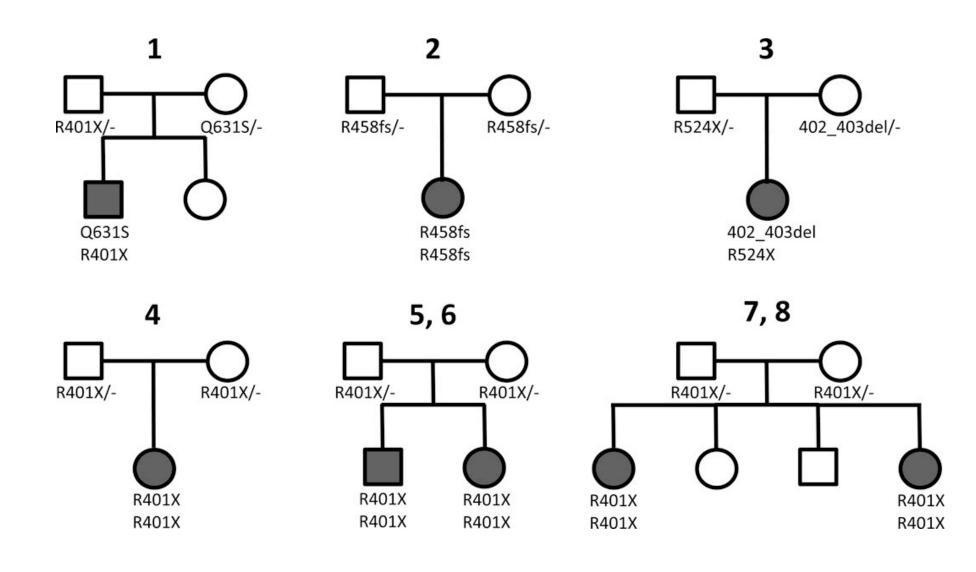


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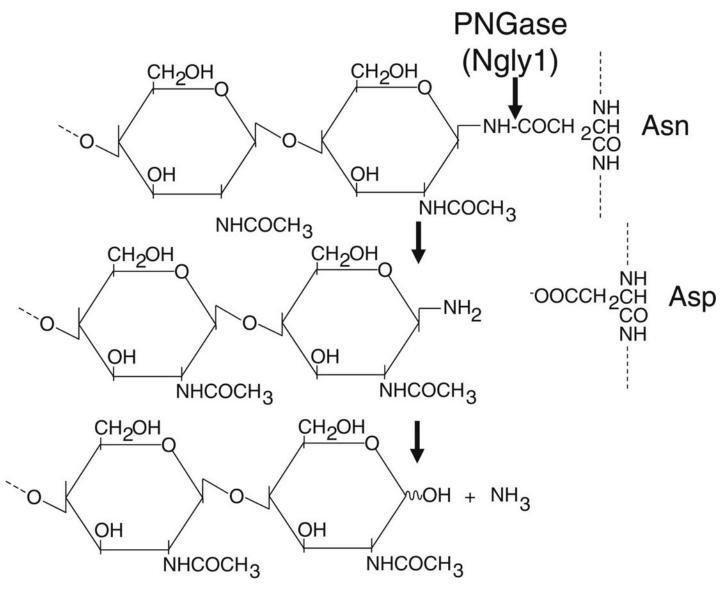


Whole Exome Sequencing: Mutations in NGLY1 Cause an Inherited Disorder of the Endoplasmic Reticulum-Associated Degradation (ERAD) Pathway

Gregory M. Enns,...David Goldstein

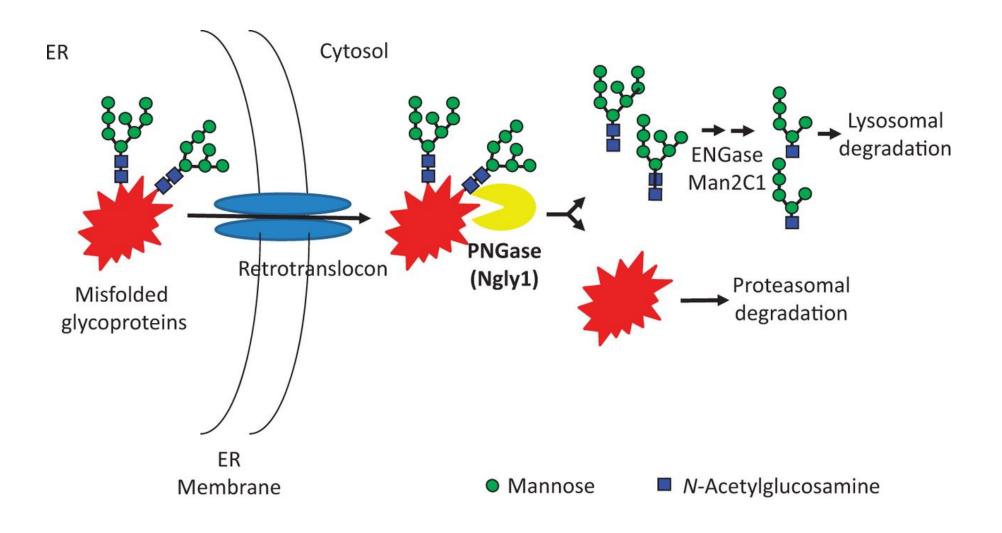


Reaction scheme of PNGase.



Suzuki T J Biochem 2015;157:23-34

The involvement of cytoplasmic PNGase in ERAD. The glycoproteins destined for degradation are translocated from the ER lumen to the cytosol.



Suzuki T J Biochem 2015;157:23-34

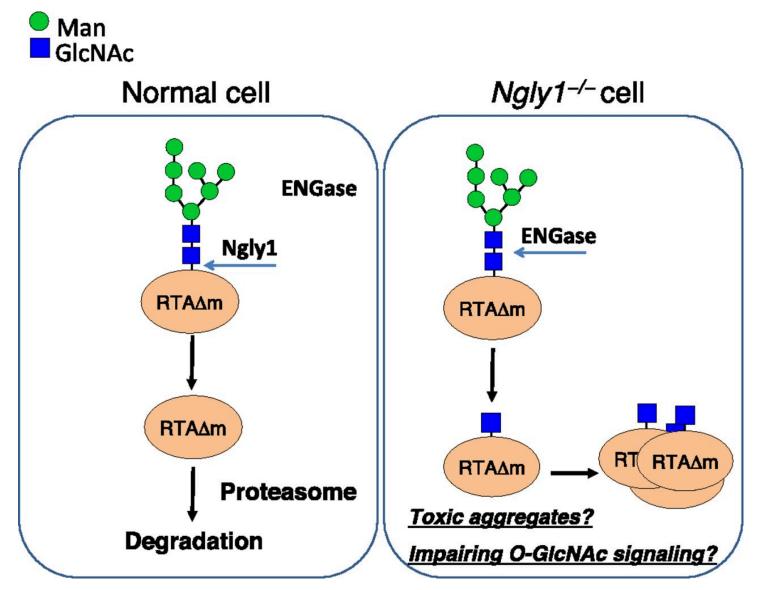


NGLY1 description for NGLY1.org

"We are fortunate that N-Glycanase was studied by the glycobiology community long before the discovery of the disorder."

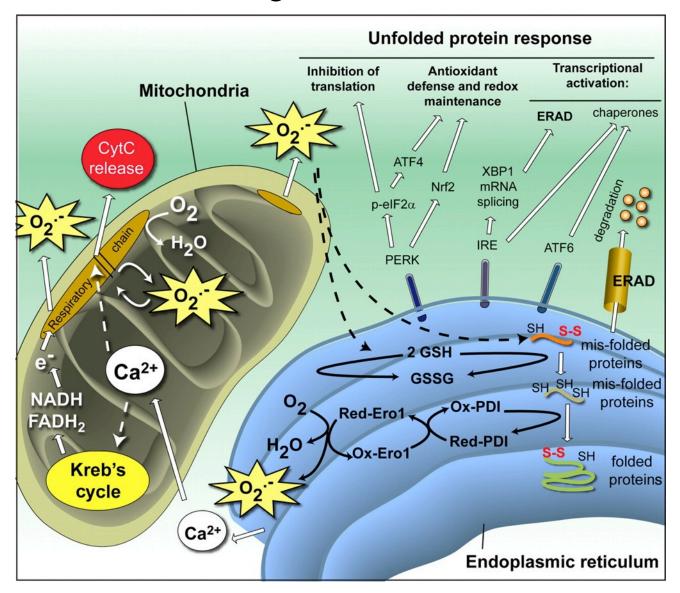
- N-Glycanase (encoded by the gene NGLY1) is responsible for cleaving N-linked glycans from misfolded glycoproteins, so that the body can recycle them.
- Lacking N-Glycanase leaves the body with an impaired capacity to recycle misfolded glycoproteins, which appear to accumulate in the cells of patients.
- The current hypothesis is that accumulation of these misfolded glycoproteins is what causes the harm in these patients.

Schematic representation of ENGase-mediated formation of N-GlcNAc proteins in Ngly1-/- cells.



Huang C et al. PNAS 2015;112:1398-1403

ROS generation by the ER and its interrelations to mitochondrial ROS generation.



Bashan N et al. Physiol Rev 2009;89:27-71

Physiological Reviews

Clinical Features of NGLY1 deficiency

In addition to global developmental delay, neurological impairment, movement disorder and hypotonia, there are some symptoms that only appear in subgroups of the patient population.

Each of the following symptoms has been found in at least half of all patients:

- A lack of tears
- Liver dysfunction: In particular, alpha-fetoprotein (AFP) may be extremely elevated while young.
- A smaller head (around the 5th percentile).
- Diminished reflexes
- **material stored in liver cells**: There appears to be something stored in the cytoplasm of liver cells.
- **Seizures**: About half of all patients have observable seizures. Patient EEGs are often described as "abnormal."

ORIGINAL ARTICLE

Clinical application of exome sequencing in undiagnosed genetic conditions

```
Anna C Need, Vandana Shashi, Yuki Hitomi, Kelly Schoch, David B Goldstein, Kevin V Shianna, Marie T McDonald, Miriam H Meisler, David B Goldstein,
```

J Med Genet 2012;49:353-361

 Table 1
 Demographic and clinical features of sequenced patients

Raca

Trio

Cav

1110	Sex	Aye	nace	Symptoms
2	M	3	European-American	Developmental delay, multifocal epilepsy, involuntary movements, abnormal liver function, absent tears

Cumptome

J Med Genet 2012;49:353-361

ORIGINAL RESEARCH ARTICLE



1st disorder of DE-Glycosylation

Mutations in NGLY1 cause an inherited disorder of the endoplasmic reticulum-associated degradation pathway

Gregory M. Enns, MB, ChB¹, Vandana Shashi, MD, MBBS², Matthew Bainbridge, PhD³, Michael J. Gambello, MD, PhD⁴, Farah R. Zahir, PhD⁵, Thomas Bast, MD⁶, Rebecca Crimian, MS², Kelly Schoch, MS², Julia Platt, MS¹, Rachel Cox, MS¹, Jonathan A. Bernstein, MD, PhD¹, Mena Scavina, DO⁷, Rhonda S. Walter, MD®, Audrey Bibb, MS⁴, Melanie Jones, PhD⁴, Madhuri Hegde, PhD⁴, Brett H. Graham, MD, PhD³, Anna C. Need, PhD⁰, Angelica Oviedo, MD¹⁰, Christian P. Schaaf, MD, PhD³¹¹, Sean Boyle, PhD¹², Atul J. Butte, MD, PhD¹², Rong Chen, PhD¹², Michael J. Clark, PhD¹², Rajini Haraksingh, PhD¹², Tina M. Cowan, PhD¹³, FORGE Canada Consortium, Ping He, MD, PhD¹⁴, Sylvie Langlois, MD⁵, Huda Y. Zoghbi, MD³,¹¹¹,¹⁵, Michael Snyder, PhD¹², Richard Gibbs, PhD³, Hudson H. Freeze, PhD¹⁴ and David B. Goldstein, PhD¹6,¹7

Clinical Features of NGYL1

Developmental delay (8/8) Movement disorder (8/8) Hypotonia (8/8)	Found at NIH
Alacrima/hypolacrima (7/8) EEG abnormalities (7/8) Constipation (7/8) Fransaminase elevation (6/7) Microcephaly (6/8) Decreased reflexes (6/8) Abnormal brain imaging (6/8) Abnormal liver storage (5/6) IUGR (5/8) Elevated blood lactate (4/6) Seizures (4/8) Strabismus (4/8) Corneal disease (4/8) Chalazions (4/8) Ocular apraxia (4/8) Neonatal jaundice (4/8) Dysmorphic features (4/8) Scoliosis (4/8) Small hands/feet (4/8) Peripheral neuropathy (3/3) Elevated AFP (3/5) ABR abnormalities (2/5) Liver fibrosis (2/6)	Hypolacrima on Schirmer testing (8/8) Optic nerve pallor (6/8) Mild peripheral retinal pigmentary changes (5/8) Near normal peripheral hearing sensitivity (8/9) Hyperkinetic movement disorder (9/9) Abnormal sweat response in a length dependent manner (5/8) ABR Delayed and/or dysynchronous transmission through the brainstem (7/8) History of absence/atonic/myoclonic seizures (5/9) Delayed bone age (6/8) Developmental delay (9/9) Demyelinating Axonal sensorimotor polyneuropathy (5/8) Mostly resolved transaminitis (6/9 (one liver transplant)) Abnormal liver texture on ultrasound (5/9)
	Cerebral atrophy (3/8)

Clinical Features of NGYL1

NEW Findings from NIH

Abnormal neurotransmitter levels (3/8)

Low CSF protein (6/8) and albumin levels (8/8)

Hyper immune response to the rubella and rubeola vaccination (7/8),

Lower than predicted resting energy expenditure (8/8)

Consistently affectionate and happy demeanor (8/8)

PERTINENT NEGATIVES from NIH

Normal echocardiogram

Normal gastric fluid pH

No evidence of primary muscle disease on EMG

No evidence of aspiration by Swallow study







NGLY1-CDG NIH





NGLY1-CDG NIH













